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Remarks

The claims as pending are directed to pharmaceutical formulations for oral administration of insulin. The formulations include a particulate pharmaceutical substrate with an insulin coating, where the particulate pharmaceutical substrate is free of a polysaccharide. New claims 56 and 57 have been added, specifying that the insulin is hexyl insulin monoconjugate-2 polydisperse (HIM2).

Rejections under 35 U.S.C. § 103 (a)

Claims 43-53 and 55 have been rejected under 35 U.S.C. § 103 (a) as obvious over U.S. Patent No. 5,958,458 to Norling et al. These rejections are respectfully traversed.

The Claimed Formulations

The present invention relates, in general, to oral pharmaceutical formulations containing insulin coated onto a non-polysaccharide substrate (Claims 43-53), and oral formulations containing insulin coated onto dibasic calcium phosphate (Claim 55).

The claimed formulations include a core similar to nonpareils (sugar spheres), but in this case, the cores do not include sugar. Coatings of sugar spheres with insulin would defeat the purpose of the insulin administration, and accordingly, there would be no motivation to coat sugar spheres with insulin. The present invention obtains a release rate similar to that which would be obtained using nonpareils, but avoids using sugar (and thus avoids the subsequent harm to diabetics). This point is articulated, for example, in Paragraph 7 of the specification.

Because it is not well known to administer insulin in an oral formulation, it would not have been obvious to modify nonpareil formulations to arrive at the claimed invention.

Norling

Norling teaches cores that include an active agent and an inert carrier, which cores are coated. The coatings include "a film coating, a sugar coating, a bioadhesive coating, or a so-called modified release coating." The coatings do not include an active agent such as insulin. This principle is outlined, for example, in the first few paragraphs of the Detailed Description, which state:

> "The formulation comprises individual units in the form of cores, such as, e.g., coated cores comprising:
> i) a pharmaceutically acceptable inert carrier which is present in the core in a first concentration of at least about 20% w/w calculated on the total weight of the core, and which is selected from the group consisting of calcium carbonate, calcium silicate, calcium magnesium silicate, calcium phosphate, kaolin, sodium hydrogen carbonate, sodium sulfate, barium carbonate, barium sulfate, magnesium sulfate, magnesium carbonate, and activated carbon, and
> ii) an active substance,
>
> "As mentioned above, the cores contained in a formulation according to the present invention comprise a pharmaceutically acceptable inert carrier and an active substance."
>
> "The concentration of the inert carrier in the cores depends mainly on the following two factors: i) the objective of obtaining sufficiently robust cores (in general, the robustness increases as the concentration of the inert carrier in the cores increases), and ii) the loading of active substance ...."

Analysis

The claimed invention relates to an inert core with an insulin coating. Norling relates to drug materials blended with an inert material and formed into a core, which core is subsequently coated. These two formulations would be expected to provide totally different release rates. That is, an insulin-coated calcium core would be expected to provide a more instantaneous release than a core formed from a mixture of an insulin and an inert compound.

Particles including a core formed from a calcium/insulin mixture would appear to provide a release rate based on the dissolution of insulin, as hindered by the co-dissolution of the inert core material. In contrast, the claimed insulin-coated particles delivers the insulin in the coating before the inert core is even exposed.

Because the release rates would be expected to be totally different, Norling does not teach or suggest the claimed invention, nor would it be obvious to modify Norling to arrive at the claimed invention. Since Norling specifically states that "...the cores contained in a formulation according to the present invention comprise a pharmaceutically acceptable inert carrier and an active substance," there would be no motivation to modify Norling to put the active substance on the outside of the core, rather than in the core. Norling actually teaches away from putting the active substance outside of the core. For any of these reasons, the obviousness rejection should be withdrawn.

With respect to newly added claims 56 and 57, Norling does not teach or suggest formulations that include hexyl insulin monoconjugate-2 polydisperse (HIM-2), so these claims would not be obvious over Norling.

Conclusion

It is believed that all of the claims are currently in condition for allowance. The Examiner is encouraged to contact Applicants' undersigned representative if he has any questions regarding the above.

Respectfully submitted,

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